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09/230048 INTERFERENCE search

Title: VIRAL INTERLEUKIN-6
Inventor: FLECKENSTEIN,BERNHARD

SEQ ID NO: 1
SEQ ID NO: 2
SEQ ID NO: 2 (87-105)

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TYPE OF SEARCH:
NA Sequences: ____________
AA Sequences: ____________
Structures: ____________
Bibliographic: ____________
Litigation: ____________
Full text: ____________
Patent Family: ____________
Other: ____________

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STN: ____________
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DRLink: ____________
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Sequence Sys.: ____________
WWW/Internet: ____________
Other (specify): ____________

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L4: Entry 6 of 15 File: USPT Dec 15, 1998

DOCUMENT-IDENTIFIER: US 5849564 A
TITLE: Polypeptides from Kaposi's sarcoma-associated herpesvirus, DNA encoding same and uses thereof

DEPR:
This invention provides the isolated KSHV polypeptide comprising viral interleukin 6 (vIL-6) encoded by ORF K2. In one embodiment, antibodies selectively recognizing vIL-6 allow differentiation among lymphomas.

End of Result Set

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L2: Entry 3 of 3 File: USPT Dec 15, 1998

DOCUMENT-IDENTIFIER: US 5849564 A
TITLE: Polypeptides from Kaposi's sarcoma-associated herpesvirus, DNA encoding same and uses thereof

DRPR:
FIGS. 5A-5B FIG. 5A. Immunoblot of rabbit antipeptide antibodies generated from amino acid sequences of vIL-6, THYSPPKFDR (SEQ ID NO:2) and PDVTPDVHDR (SEQ ID NO:3), against cell lysates of BCP-1, BC-1, P3HR1 cell lines with and without TPA induction (lanes 1-6), 1 .mu.g human rIL-6 (lane 7), and concentrated COS7 rvIL-6 and 6-LIv supernatants (lanes 8-9). Anti-vIL-6 antibodies specifically recognize the viral IL-6 polypeptide in both recombinant supernatants and cell lines but not human IL-6. The BCP-1 cell line constitutively expresses low levels of vIL-6 whereas polypeptide expression increases on TPA treatment for both BC-1 (KSHV and EBV coinfected) and BCP-1 (KSHV infection alone) indicating lytic phase expression. Preimmune sera from immunized rabbits did not react on immunoblotting to any of the preparations. FIG. 5B. Anti-huIL-6 monoclonal antibodies do not cross-react with cell-associated or recombinant vIL-6 preparations.

L5 ANSWER 1 OF 9 MEDLINE
AN 1999412342 MEDLINE
DN 99412342
TI Human herpesvirus 8 **interleukin-6** (vIL-6) signals through gp130 but has structural and **receptor-binding** properties distinct from those of human **IL-6**.
AU Wan X; Wang H; Nicholas J
CS Molecular Virology Laboratories, Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21231, USA.
NC R55 CA76445 (NCI)
RO1 CA76445 (NCI)
SO JOURNAL OF VIROLOGY, (1999 Oct) 73 (10) 8268-78.
Journal code: KCV. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199912
EW 19991203
AB Human herpesvirus 8 (HHV-8) has been associated with classical, endemic (African), and AIDS-related Kaposi's sarcoma (KS), body cavity-based primary effusion lymphomas, and multicentric Castleman's disease (MCD). HHV-8 encodes a functional homologue of **interleukin-6** (**IL-6**), a cytokine that promotes the growth of KS and myeloma cells and is found at elevated levels in MCD lesions and patient sera. We have previously reported that the **viral IL-6** (vIL-6) gene product can support the growth of the **IL-6**-dependent murine hybridoma cell line, B9, and that the gp80 (**IL-6 receptor** [IL-6R]) component of the **IL-6 receptor**-signal transducer (gp180) complex plays a role in mediating this activity. However, it has been shown by others that vIL-6 can function in human cells independently of IL-6R. Here we have extended our functional studies of vIL-6 by identifying transcription factors and pathways used in human Hep3B cells, investigating the utilization of gp130 and IL-6R by vIL-6, and undertaking mutational analyses of vIL-6 and gp130. The data presented here establish that vIL-6, in common with its endogenous counterparts, can mediate signal transduction through gp130 and activate multiple transcription factors, map residues within the vIL-6 protein that are and are not important for vIL-6 signalling, and identify a gp130 mutant that is nonfunctional with respect to vIL-6 signalling in the absence of IL-6R but that retains the ability to mediate vIL-6 and human **IL-6** (hIL-6) signal transduction when IL-6R is coexpressed. The data presented demonstrate functional and mechanistic similarities between vIL-6 and endogenous **IL-6** proteins but also highlight differences in the structural and **receptor-binding** properties of vIL-6 relative to its human counterpart.

Kerr, Janet
T : STIC-ILL
Subject: 09/230,048

Please order the following references for ***Janet M. Kerr, CM1/12E17, 305-4055, A.U. 1633***

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pp. 215-226
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pp. 533-542
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RB145A2356

L20 ANSWER 3 OF 20 MEDLINE
AN 1999290757 MEDLINE
DN 99290757
TI Angiogenesis and hematopoiesis induced by Kaposi's sarcoma-associated herpesvirus-encoded **interleukin-6** [see comments].
CM Comment in: Blood 1999 Jun 15;93(12):4031-3
AU Aoki Y; Jaffe E S; Chang Y; Jones K; Teruya-Feldstein J; Moore P S; Tosato G
CS Division of Hematologic Products, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD, USA.. AOKI@CBER.FDA.GOV
SO BLOOD, (1999 Jun 15) 93 (12) 4034-43.
Journal code: A8G. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199909
EW 19990901
AB Kaposi's sarcoma-associated herpesvirus (KSHV; also known as human herpesvirus 8 [HHV-8]) is a herpesvirus linked to the development of Kaposi's sarcoma (KS), primary effusion lymphoma, and a proportion of Castleman's disease. KSHV encodes viral **interleukin-6** (vIL-6), which is **structurally homologous** to human and murine IL-6. The biological **activities** of vIL-6 are largely unknown. To gain insight into the biology of vIL-6, we expressed vIL-6 in murine fibroblasts NIH3T3 cells and inoculated stable vIL-6-producing clones into athymic mice. vIL-6 was detected selectively in the blood of mice injected with vIL-6-expressing clones. Compared with controls, vIL-6-positive mice displayed increased hematopoiesis in the myeloid, erythroid, and megakaryocytic lineages; plasmacytosis in spleen and lymph nodes; hepatosplenomegaly; and polyclonal hypergammaglobulinemia. vIL-6-expressing NIH3T3 cells gave rise to tumors more rapidly than did control cells, and vIL-6-positive tumors were more vascularized than controls. Vascular endothelial growth factor (VEGF) was detected at higher levels in the culture supernatant of vIL-6-expressing cells compared with controls, and immunohistochemical staining detected VEGF in spleen, lymph nodes, and tumor tissues from mice bearing vIL-6-producing tumors but not control tumors. Thus, vIL-6 is a multifunctional cytokine that promotes hematopoiesis, plasmacytosis, and angiogenesis. Through these **functions**, vIL-6 may play an important role in the pathogenesis of certain KSHV-associated disorders.

L20 ANSWER 1 OF 20 MEDLINE
AN 2000030867 MEDLINE
DN 20030867
TI KSHV-encoded viral IL-6 activates multiple human IL-6 signaling pathways.
AU Osborne J; Moore P S; Chang Y
CS Department of Pathology, Columbia University College of Physicians and Surgeons, New York, NY 10027, USA.
NC R01-CA76586 (NCI)
SO HUMAN IMMUNOLOGY, (1999 Oct) 60 (10) 921-7.
Journal code: G9W. ISSN: 0198-8859.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200002
EW 20000204
AB Kaposi's sarcoma-associated herpesvirus (KSHV or HHV8) encodes a **structural** and **functional homologue** of human IL-6 called viral IL-6 (vIL-6). Expression of vIL-6 in KSHV-related lymphoproliferative disorders has been implicated in their pathogenesis. vIL-6 has been shown to mimic a number of IL-6 **activities** including stimulating the growth of IL-6 dependent cell lines and activating the JAK1 and STAT1/3 pathway in HepG2 cells. However, IL-6 and vIL-6 display differences in receptor usage that may give rise to underlying qualitative and quantitative differences in the signaling pathways utilized. While IL-6 has an absolute requirement for both the IL-6 Ralpha and the gp130 subunits, vIL-6 appears to require only gp130. In addition to JAK1 and STAT1/3 pathways, IL-6 activates multiple other pathways including the direct activation of STAT 5 by JAK1, the Ras-MAP kinase cascade and a novel H7-sensitive pathway. In this study we examined whether vIL-6 is capable of signaling via distinct IL-6 response elements (IL-6 RE) under the control of these different pathways. We show that vIL-6 activates both STAT1/3- and STAT5-dependent Type II IL-6 REs. In addition, vIL-6 induces transcriptional activation via a Type I IL-6 RE that binds C/EBP, indicative of Ras-MAP kinase pathway induction. Furthermore, vIL-6 is capable of activating the IL-6 response element in the c-jun promoter (RE-IL-6). vIL-6 induced activation of JRE-IL-6 requires both the Ets- and Cre-like sites, suggesting that vIL-6 is capable of stimulating the same novel serine/threonine kinase mediated pathway as IL-6. These results demonstrate that vIL-6 can stimulate all of the known IL-6-induced signaling pathways. Therefore, vIL-6 could potentially contribute to KSHV-related disease progression by continued activation of IL-6-stimulated growth and anti-apoptotic pathways even when cells attempt to protect themselves from IL-6 over-stimulation by downmodulating their IL-6Ralpha subunits.

L20 ANSWER 8 OF 20 MEDLINE
AN 97289981 MEDLINE
DN 97289981
TI **Interleukin-6: structure-function** relationships.
AU Simpson R J; Hammacher A; Smith D K; Matthews J M; Ward L D
CS Joint Protein Structure Laboratory, Ludwig Institute for Cancer Research, (Melbourne Tumour Biology Branch), Parkville, Victoria, Australia.. simpson@licre.ludwig.edu.au
SO PROTEIN SCIENCE, (1997 May) 6 (5) 929-55. Ref: 338
Journal code: BNW. ISSN: 0961-8368.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
OS GENBANK-Y00081; GENBANK-L26032; GENBANK-L26028; GENBANK-L46804; GENBANK-L34165; GENBANK-U12234; GENBANK-L46802; GENBANK-D13227; GENBANK-M80258; GENBANK-L46803; GENBANK-X57317; GENBANK-X68723; GENBANK-M24221; GENBANK-M26744
EM 199711
AB **Interleukin-6** (IL-6) is a multifunctional cytokine that plays a central role in host defense due to its wide range of immune and hematopoietic **activities** and its potent ability to induce the acute phase response. Overexpression of IL-6 has been implicated in the pathology of a number of diseases including multiple myeloma, rheumatoid arthritis, Castleman's disease, psoriasis, and post-menopausal osteoporosis. Hence, selective antagonists of IL-6 action may offer therapeutic benefits. IL-6 is a member of the family of cytokines that includes interleukin-11, leukemia inhibitory factor, oncostatin M, cardiotrophin-1, and ciliary neurotrophic factor. Like the other members of this family, IL-6 induces growth or differentiation via a receptor-system that involves a specific receptor and the use of a shared signaling subunit, gp130. Identification of the regions of IL-6 that are involved in the interactions with the IL-6 receptor, and gp130 is an important first step in the rational manipulation of the effects of this cytokine for therapeutic benefit. In this review, we focus on the sites on IL-6 which interact with its low-affinity specific receptor, the IL-6 receptor, and the high-affinity converter gp130. A tentative model for the IL-6 hexameric receptor ligand complex is presented and discussed with respect to the mechanism of action of the other members of the IL-6 family of cytokines.

L20 ANSWER 11 OF 20 MEDLINE
AN 96075789 MEDLINE
DN 96075789
TI **Functional** distinction of two regions of human **interleukin 6** important for signal transduction via gp130.
AU de Hon F D; ten Boekel E; Herrman J; Clement C; Ehlers M; Taga T; Yasukawa K; Ohsugi Y; Kishimoto T; Rose-John S; et al
CS Department of Autoimmune Diseases, Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam.
SO CYTOKINE, (1995 Jul) 7 (5) 398-407.
Journal code: A52. ISSN: 1043-4666.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199602
AB Mutagenesis of a region of human interleukin (IL)-6 which is important for triggering signal transduction via the IL-6 receptor beta-chain (gp130) has lead to the isolation of a variant of human IL-6 (IL-6.Q160E/T163P), which could antagonize the biological **activity** of wild type IL-6 on the human EBV transformed B cell line CESS and the human hepatoma cell line HepG2. Surprisingly this antagonistic IL-6 variant had an agonistic effect on the human myeloma cell line XG-1, albeit at a 1000-fold higher concentration than wild type IL-6. This residual **activity** of the mutant arose from triggering gp130, because it could be inhibited by a gp130 specific mAb. Extensive mutagenesis of residues between Q153 and H165 of human IL-6, a region which is partly **homologous** in cytokines which also signal via gp130 (oncostatin M, ciliary neurotrophic factor, leukaemia inhibitory factor, IL-11), did result in the isolation of a second antagonist for IL-6 **activity** on CESS and HepG2 cells. However on XG-1 cells this variant was active as well. These results suggest that (an) additional region(s) of the IL-6 molecule might be involved in gp130 triggering. Recently we indeed found that residues Lys42-Ala57 are also important for gp130 triggering. Inhibition experiments with neutralizing IL-6R alpha-chain specific mAb show that this region can be **functionally** separated from the Q153-H165 region. These findings have important implications for the development of receptor antagonists of IL-6 and IL-6 family members.

QP551.P697

L20 ANSWER 15 OF 20 MEDLINE
AN 95276635 MEDLINE
DN 95276635
TI **Structure-function** analysis of human IL-6: identification of two distinct regions that are important for receptor binding.
AU Hammacher A; Ward L D; Weinstock J; Treutlein H; Yasukawa K; Simpson R J
CS Joint Protein Structure Laboratory, Ludwig Institute for Cancer Research/Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia.
SO PROTEIN SCIENCE, (1994 Dec) 3 (12) 2280-93.
Journal code: BNW. ISSN: 0961-8368.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199509
AB **Interleukin-6** (IL-6) is a multifunctional cytokine that plays an important role in host defense. It has been predicted that IL-6 may fold as a 4 alpha-helix bundle **structure** with up-up-down-down topology. Despite a high degree of sequence similarity (42%) the human and mouse IL-6 polypeptides display distinct species-specific **activities**. Although human IL-6 (hIL-6) is active in both human and mouse cell assays, mouse IL-6 (mIL-6) is not active on human cells. Previously, we demonstrated that the 5 C-terminal residues of mIL-6 are important for **activity**, conformation, and stability (Ward LD et al., 1993, Protein Sci 2:1472-1481). To further probe the **structure-function** relationship of this cytokine, we have constructed several human/mouse IL-6 hybrid molecules. Restriction endonuclease sites were introduced and used to ligate the human and mouse sequences at junction points situated at Leu-62 (Lys-65 in mIL-6) in the putative connecting loop AB between helices A and B, at Arg-113 (Val-117 in mIL-6) at the N-terminal end of helix C, at Lys-150 (Asp-152 in mIL-6) in the connecting loop CD between helices C and D, and at Leu-178 (Thr-180 in mIL-6) in helix D. Hybrid molecules consisting of various combinations of these fragments were constructed, expressed, and purified to homogeneity. The conformational integrity of the IL-6 hybrids was assessed by far-UV CD. Analysis of their biological **activity** in a human bioassay (using the HepG2 cell line), a mouse bioassay (using the 7TD1 cell line), and receptor binding properties indicates that at least 2 regions of hIL-6, residues 178-184 in helix D and residues 63-113 in the region incorporating part of the putative connecting loop AB through to the beginning of helix C, are critical for efficient binding to the human IL-6 receptor. For human IL-6, it would appear that interactions between residues Ala-180, Leu-181, and Met-184 and residues in the N-terminal region may be critical for maintaining the **structure** of the molecule; replacement of these residues with the corresponding 3 residues in mouse IL-6 correlated with a significant loss of alpha-helical content and a 200-fold reduction in **activity** in the mouse bioassay. A **homology** model of mIL-6 based on the X-ray **structure** of human granulocyte colony-stimulating factor is presented.

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L20 ANSWER 12 OF 20 MEDLINE
AN 95386687 MEDLINE
DN 95386687
TI AIDS-associated Kaposi's sarcoma (KS) cells express oncostatin M (OM)-specific receptor but not leukemia inhibitory factor/OM receptor or **interleukin-6** receptor. Complete block of OM-induced KS cell growth and OM binding by anti-gp130 antibodies.
AU Murakami-Mori K; Taga T; Kishimoto T; Nakamura S
CS Institute of Molecular Medicine and Technology, Huntington Memorial Hospital, Pasadena, California 91105, USA.
SO JOURNAL OF CLINICAL INVESTIGATION, (1995 Sep) 96 (3) 1319-27. Journal code: HS7. ISSN: 0021-9738.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199512
AB Oncostatin M (OM), which shares **functional** similarity and **structural homology** to leukemia inhibitory factor (LIF) and **interleukin-6** (IL-6), **functions** as a potent growth factor for AIDS-associated Kaposi's sarcoma-derived cells (AIDS-KS cells). OM was also suggested to bind to the LIF receptor (LIF/OM receptor), which consists of a signal transducing subunit for LIF and IL-6 (gp130) and a LIF receptor alpha-subunit. Recent studies indicate that IL-6 has growth-stimulating **activity** for AIDS-KS cells. However, we find that AIDS-KS cell growth is exclusively induced by OM and not by LIF or IL-6. We also observed the lack of binding properties of AIDS-KS cells for LIF and IL-6. Scatchard plots revealed the existence of two affinity classes of OM receptor sites on AIDS-KS cells, with Kd values of 6-12 pM (high affinity) and 521-815 pM (low affinity). In competition binding studies, we find that the OM-specific receptor, but not the LIF/OM receptor, contributes to the OM-specific growth stimulation of AIDS-KS cells. We also noted that anti-gp130 antibodies can completely abolish OM-induced growth stimulation of AIDS-KS cells as well as OM binding to AIDS-KS cells. PCR amplification clearly revealed high levels of gp130 expression in AIDS-KS cells, while the transcript of LIF receptor alpha-subunit or IL-6 receptor alpha-subunit was not observed. Therefore, we conclude that (a) AIDS-KS cells express the OM-specific receptor with high and low affinity, but not the LIF/OM receptor; (b) gp130 on AIDS-KS cells plays a key role in OM binding and signaling on the OM-specific receptor; and (c) the lack of biological response of AIDS-KS cells to IL-6 and LIF can be explained by the absence of the IL-6 and LIF/OM receptors. All this evidence shows the correlation of OM-specific biological **activity** with expression of the OM-specific receptor and the involvement of gp130 on this receptor, as based on findings in in vitro growth assays and binding experiments for AIDS-KS cells.